This Program Announcement expires on November 30, 2004 unless reissued.

PATHOGENESIS AND TREATMENT OF INFLAMMATORY MUSCLE DISEASE

Release Date: August 31, 2001

PA NUMBER: PA-01-131

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Neurological Disorders and Stroke
National Institute of Dental and Craniofacial Research

THIS PA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. MODULAR INSTRUCTIONS MUST BE USED FOR RESEARCH GRANT APPLICATIONS UP TO $250,000 PER YEAR. MODULAR BUDGET INSTRUCTIONS ARE PROVIDED IN SECTION C OF THE PHS 398 (REVISION 5/2001) AVAILABLE AT http://grants.nih.gov/grants/funding/phs398/phs398.html.

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Dental and Craniofacial Research (NIDCR) encourage investigator-initiated research grant applications on pathogenesis and treatment of inflammatory myopathy. Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients with any form of inflammatory muscle disease.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS led national activity for setting priority areas. This PA is related to one or more of the priority areas. This program announcement, Pathogenesis and Treatment of Inflammatory Muscle Disease, is related to the priority area chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the Federal government. Racial/ethnic minority ndividuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

The mechanism of support will be the individual research project grant (R01). The Principal Investigator or program director, as well as any participating investigators, will plan, direct, and perform the research. The total project period for an application submitted in response to this program announcement may not exceed five years.

Applicants must receive permission from the NIAMS, or NINDS, or NIDCR prior to the submission of an application requesting more than $500,000 in direct costs per year for any year of the proposed study.

Investigators should contact program staff listed under INQUIRIES to discuss applications using other mechanisms, such as the program project grant.

RESEARCH OBJECTIVES

Background

Inflammatory myopathies encompass a number of differing conditions (dermatomyositis, polymyositis, inclusion body myositis) characterized by muscle inflammation and repeated tissue degeneration and regeneration. In general myositis is known to result in muscle weakness in affected individuals. While myositis has been classified as an autoimmune disease, little is known about the etiology of this condition. One condition, sporadic inclusion-body myositis (IBM), appears to share pathological features with some neurodegenerative disorders. IBM demonstrates accumulations of beta/A4 amyloid proteins similar to accumulations of amyloid in brains of Alzheimer disease. Current therapies for myositis remain broad based and relatively nonspecific. These include corticosteroids, cytotoxic agents, and immunosuppressives.

Although there have been tremendous advances on the understanding of the cell biology, physiology and molecular genetics of skeletal muscle, there is a paucity of information about how the normal function of muscle cells is affected by inflammatory processes. Further, the

contribution of the skeletal muscle cells or the neural innervation of the muscle to the inflammatory process by either expression of surface molecules or release of soluble mediators or structural components that may activate an immune or inflammatory response is not well understood.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Neurological Disorders and Stroke, and the Office of Rare Diseases of the National Institutes of Health (NIH) cosponsored a "Workshop on Inflammatory Myopathy." The purpose of the workshop was to stimulate new research on this uncommon and understudied family of diseases. Investigators from around the world, representing several biomedical disciplines, discussed what is currently known in various disciplines relevant to inflammatory myopathy and suggested new areas for research support. A summary of the workshop may be found at: http://www.nih.gov/niams/reports/myoreportsummary.htm

Scope and Objectives

The purpose of this initiative is to encourage studies on inflammatory myopathies and the role of inflammation in muscle disease. Cellular processes should be examined, including mechanisms of cell injury and the role of cytokines. It is important to define the borders between inflammatory myopathy and genetic dystrophies that appear clinically similar. Since inflammatory cells are present in muscles in most human dystrophies, more research is needed on the extent to which muscle cells play a role as antigen-presenting cells. There is a need for further research on the role of inflammation and inflammatory cells in muscular dystrophy. It is important to determine if inflammatory processes interfere with repair of damaged muscle.

A goal of this initiative is to promote research that will lead to better treatment for inflammatory muscle disease. Researchers are encouraged to propose studies aimed at developing and refining outcomes measures, studies looking at long term outcomes, new therapeutic interventions. Important research priorities include studies on gene and stem cell therapies, pharmacological approaches to treatment, and clarification of inflammatory mechanisms in muscle.

Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients. Investigators with diverse scientific interests are invited to apply their expertise to basic, applied, and clinical research to enhance our understanding of the pathogenesis and treatment of inflammatory muscle disease, including the development and sharing of appropriate resources, including animal models.

Examples that illustrate possible areas of research are presented below. They are intended only to provide a broad direction for research and should be considered illustrative and not restrictive.

o Clarification of the processes by which muscle cells are damaged and repaired in the inflammatory myopathies.

o Delineation of the molecular basis for differences in repair between masticatory and somatic musculature.

o Exploration of immune responses in muscle diseases.

o Studies that establish and clarify the role of cell mediated and antibody mediated immune responses to muscle substances and muscle related structures.

o Clarification of molecular and cellular aspects of tissue degeneration in inflammatory muscle disease.

o Studies aimed at exploring pathogenetic mechanisms involving mitochondrial dysfunction and oxidative stress.

o Deeper exploration of the role of inflammation in genetic muscle diseases.

o Delineation of the potential role of neurogenic influences in the origin of inflammatory muscle disease.

o Studies that help define standard approaches to evaluate disease activity, disease damage, and clinical outcomes.

o Studies that help develop improved diagnostic procedures.

o Using improved imaging techniques to better understand mechanisms of inflammatory muscle disease and monitor treatment.

o Exploration of new types of therapy, including gene transfer and use of muscle stem cells.

o Exploration of pharmacologic interventions, including evaluations of the use of steroids.

o Development, use, and sharing of appropriate animal models for inflammatory muscle disease.

o Study the involvement of apoptotic cell death in the process of muscle fiber degeneration.

o Explore the relationship between inflammatory cells, muscle cell death, and blood vessels.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm: The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at: http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the

application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

APPLICATION PROCEDURES

The PHS 398 research grant application instructions and forms (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html are to be used in applying for these grants and will be accepted at the standard application deadlines (http://grants.nih.gov/grants/dates.htm) as indicated in the application kit. This version of the PHS 398 is available in an interactive, searchable PDF format. Although applicants are encouraged to begin using the 5/2001 revision of the PHS 398 as soon as possible, the NIH will continue to accept applications prepared using the 4/1998 revision until January 9, 2002. Beginning January 10, 2002, however, the NIH will return applications that are not submitted on the 5/2001 version. For further assistance contact GrantsInfo, Telephone 301/435-0714, Email: GrantsInfo@nih.gov.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e., as plans for the study are being developed. Furthermore, the application must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application. This policy requires an applicant to obtain agreement for acceptance of any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://grants.nih.gov/grants/guide/notice-files/not98-030.html

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and NIH staff. The research grant application form PHS 398 (rev. 5/2001) at

http://grants.nih.gov/grants/funding/phs398/phs398.html is to be used in applying for these grants, with modular budget instructions provided in Section C of the application instructions. Applicants are permitted, however, to use the 4/1998 revision of the PHS 398 for scheduled application receipt dates until January 9, 2002. If you are preparing an application using the 4/1998 version, please refer to the step-by-step instructions for Modular Grants available at http://grants.nih.gov/grants/funding/modular/modular.htm. Additional information about Modular Grants is also available on this site.

GENERAL INSTRUCTIONS

The title (Pathogenesis and Treatment of Inflammatory Muscle Disease) and number of the program announcement must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, plus five signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written review, comments on the

following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

o Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

o Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

o Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

o Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

o Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

o Review of grants with foreign components will consider availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries which are not readily available in the United States or which provide augmentation of existing United States resources.

AWARD CRITERIA

Applications will compete for available funds with all other recommended applications. The following will be used in making funding decisions:

o Scientific and technical merit of the proposed project as determined by peer review

o Availability of funds

o Program balance among research areas of the announcement

NIAMS funding policy may be seen at: http://www.nih.gov/niams/grants/payline2.htm. NINDS funding strategy may be found at: http://www.ninds.nih.gov/funding/ninds_funding_strategy.htm.

INQUIRIES

Inquiries concerning this PA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic and scientific issues to one of the following persons:

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FAX: (301) 480-4543

Email: LymnR@mail.nih.gov

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
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Email: gio.zhang@nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases

45 Center Drive, Room 5AS-49F, MSC 6500
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846 (NIAMS), No. 93.853 (NINDS), and No. 93.121 (NIDCR). Awards are made under authorization of sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke free workplace and promote the non-use of all tobacco products. In addition, Public law 103-227, the pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a

facility) in which regular or routine education, library, day care, health care or early childhood development services are provided children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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